



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification <sup>6</sup> : <b>A61K 31/40, 31/405, 31/70, 31/71</b>		A1	(11) International Publication Number: <b>WO 95/17181</b> (43) International Publication Date: <b>29 June 1995 (29.06.95)</b>
(21) International Application Number: <b>PCT/EP94/03664</b> (22) International Filing Date: <b>8 November 1994 (08.11.94)</b>		(81) Designated States: AU, BY, CA, HU, JP, KR, KZ, NO, PL, RU, UA, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).	
(30) Priority Data: <b>9326136.0</b> 22 December 1993 (22.12.93) GB		<b>Published</b> <i>With international search report.</i>	
(71) Applicant: <b>PHARMACIA S.P.A. [IT/IT]; Via Robert Koch 1.2., I-20152 Milan (IT).</b>			
(72) Inventors: <b>BUZZETTI, Franco; Via della Gallarana, 4, I-20052 Monza (IT). LONGO, Antonio; Via Porpora, 160, I-20131 Milan (IT). BRASCA, Maria, Gabriella; Via Dante Alighieri, 15, I-20090 Cusago (IT). ORZI, Fabrizio; Via Angera, 10, I-20125 Milan (IT). CRUGNOLA, Angelo; Via Ruggiero Settimo, 30, I-21100 Varese (IT). BALLINARI, Dario; Via Jannozzi, 8, I-20097 San Donato Milanese (IT). MARIANI, Mariangela; Via Milano, 298/A, I-20033 Desio (IT).</b>			
(54) Title: <b>BIOLOGICALLY ACTIVE 3-SUBSTITUTED OXINDOLE DERIVATIVES USEFUL AS ANTI-ANGIOGENIC AGENTS</b>			
(57) Abstract			
<p>The new use of a compound of formula (I) wherein Y is a bicyclic ring selected from naphthalene, tetralin, quinoline, isoquinoline and indole; n is zero or an integer of 1 to 3; R<sub>1</sub> is hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl or C<sub>2</sub>-C<sub>6</sub> alkanoyl; R<sub>2</sub> is hydrogen, halogen, C<sub>1</sub>-C<sub>6</sub> alkyl, cyano, carboxy, nitro, or NHR, wherein R is hydrogen or C<sub>1</sub>-C<sub>6</sub> alkyl; R<sub>3</sub> is hydrogen or C<sub>1</sub>-C<sub>6</sub> alkyl; R<sub>4</sub> is hydrogen, hydroxy, C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>2</sub>-C<sub>6</sub> alkanoyloxy, carboxy, nitro or NHR, wherein R is as defined above; R<sub>5</sub> is hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl or halogen; or a pharmaceutically acceptable salt thereof; and wherein when Y is naphthalene then n is zero or an integer of 1 to 3, whereas when Y is tetralin, quinoline, isoquinoline or indole then n is zero, 1 or 2; and wherein when the bicyclic ring Y is naphthalene, quinoline, isoquinoline or indole, then each of the substituents OR<sub>1</sub>, R<sub>2</sub> and oxindolylidene may be independently on either of the aryl or heteroaryl moieties of said bicyclic ring, whereas only the benzene moiety is substituted when Y is tetralin; and wherein when Y is naphthalene, tetralin, quinoline or isoquinoline, then R<sub>2</sub> is hydrogen, halogen, cyano or C<sub>1</sub>-C<sub>6</sub> alkyl and R<sub>3</sub>, R<sub>4</sub> and R<sub>5</sub> are hydrogen; whereas when Y is indole, then R<sub>2</sub> is hydrogen, halogen, C<sub>1</sub>-C<sub>6</sub> alkyl, cyano, carboxy, nitro or -NHR, in which R is as defined above, R<sub>3</sub> is hydrogen or C<sub>1</sub>-C<sub>6</sub> alkyl, R<sub>4</sub> is hydrogen, hydroxy, C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>2</sub>-C<sub>6</sub> alkanoyloxy, carboxy, nitro or -NHR, wherein R is as defined above, and R<sub>5</sub> is hydrogen, halogen or C<sub>1</sub>-C<sub>6</sub> alkyl; as anti-angiogenic agent is disclosed.</p>			

**FOR THE PURPOSES OF INFORMATION ONLY**

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	GB	United Kingdom	MR	Mauritania
AU	Australia	GE	Georgia	MW	Malawi
BB	Barbados	GN	Guinea	NE	Niger
BR	Belgium	GR	Greece	NL	Netherlands
BF	Burkina Faso	HU	Hungary	NO	Norway
BG	Bulgaria	IE	Ireland	NZ	New Zealand
BJ	Benin	IT	Italy	PL	Poland
BR	Brazil	JP	Japan	PT	Portugal
BY	Belarus	KE	Kenya	RO	Romania
CA	Canada	KG	Kyrgyzstan	RU	Russian Federation
CF	Central African Republic	KP	Democratic People's Republic of Korea	SD	Sudan
CG	Congo	KR	Republic of Korea	SE	Sweden
CH	Switzerland	KZ	Kazakhstan	SI	Slovenia
CI	Côte d'Ivoire	LI	Liechtenstein	SK	Slovakia
CM	Cameroon	LK	Sri Lanka	SN	Senegal
CN	China	LU	Luxembourg	TD	Chad
CS	Czechoslovakia	LV	Latvia	TG	Togo
CZ	Czech Republic	MC	Monaco	TJ	Tajikistan
DE	Germany	MD	Republic of Moldova	TT	Trinidad and Tobago
DK	Denmark	MG	Madagascar	UA	Ukraine
ES	Spain	ML	Mali	US	United States of America
FI	Finland	MN	Mongolia	UZ	Uzbekistan
FR	France			VN	Viet Nam
GA	Gabon				

-1-

**BIOLOGICALLY ACTIVE 3-SUBSTITUTED OXINDOLE DERIVATIVES  
USEFUL AS ANTI-ANGIOGENIC AGENTS**

The present invention relates to the use of 3-  
5 substituted oxindole derivatives as angiogenesis  
inhibitors.

As known, angiogenesis, i.e. the growth of new blood  
vessels, is an essential component in the development of  
several pathological conditions in mammals, for instance  
10 chronic inflammation, diabetic retinopathy, psoriasis,  
rheumatoid arthritis, solid tumor growth and development  
of metastases.

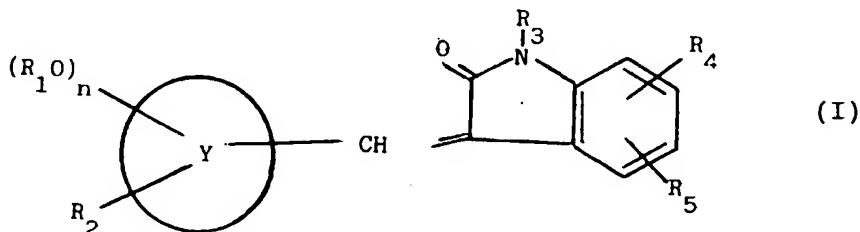
Accordingly, there is a need in therapy for drugs able  
to suppress the growth of new blood vessels.  
15 WO 91/13055 and WO 93/01182 provide in their complex  
aryl- and heteroaryl-methylene derivatives having  
tyrosine kinase inhibition activity.

Accordingly, these prior art compounds can be useful in  
the treatment of cancer and other pathological  
20 proliferative conditions, typically in inhibiting the  
development of the atheromatous plaque in mammals.

Now we have found that a selected class of known  
compounds according to WO 91/13055 and WO 93/01182 are  
active as angiogenesis inhibitors.

25 Accordingly, the present invention relates to the use of  
a compound of formula (I)

-2-



wherein

Y is a bicyclic ring selected from naphthalene, tetralin, quinoline, isoquinoline and indole;

5 n is zero or an integer of 1 to 3;

R<sub>1</sub> is hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl or C<sub>2</sub>-C<sub>6</sub> alkanoyl;

R<sub>2</sub> is hydrogen, halogen, C<sub>1</sub>-C<sub>6</sub> alkyl, cyano, carboxy, nitro, or NHR, wherein R is hydrogen or C<sub>1</sub>-C<sub>6</sub> alkyl;

R<sub>3</sub> is hydrogen or C<sub>1</sub>-C<sub>6</sub> alkyl;

10 R<sub>4</sub> is hydrogen, hydroxy, C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>2</sub>-C<sub>6</sub> alkanoyloxy, carboxy, nitro or NHR, wherein R is as defined above;

R<sub>5</sub> is hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl or halogen; or a pharmaceutically acceptable salt thereof;

and wherein when Y is naphthalene then n is zero or an integer of 1 to 3, whereas when Y is tetralin, quinoline, isoquinoline or indole then n is zero, 1 or 2;

15 and wherein when the bicyclic ring Y is naphthalene, quinoline, isoquinoline or indole then each of the substituents OR<sub>1</sub>, R<sub>2</sub> and oxindolylidene may be independently on either of the aryl or heteroaryl moieties of said bicyclic ring, whereas only the benzene moiety is substituted when Y is tetralin;

20 and wherein when Y is naphthalene, tetralin, quinoline

-3-

or isoquinoline, then  $R_2$  is hydrogen, halogen, cyano or  $C_1$ - $C_6$  alkyl and  $R_3$ ,  $R_4$  and  $R_5$  are hydrogen; whereas when  $Y$  is indole, then  $R_2$  is hydrogen, halogen,  $C_1$ - $C_6$  alkyl, cyano, carboxy, nitro or  $-NHR$  in which  $R$  is as defined above,  $R_3$  is hydrogen or  $C_1$ - $C_6$  alkyl,  $R_4$  is hydrogen, hydroxy,  $C_1$ - $C_6$  alkoxy,  $C_2$ - $C_6$  alkanoyloxy, carboxy, nitro or  $-NHR$  wherein  $R$  is as defined above, and  $R_5$  is hydrogen, halogen or  $C_1$ - $C_6$  alkyl; in the preparation of a medicament for use as anti-angiogenic agent.

10 The present invention also provides a compound of formula (I), as defined above, or a pharmaceutically acceptable salt thereof, for use in the inhibition of angiogenesis in mammals, including humans.

Object of the present invention is also to provide a

15 pharmaceutical composition having anti-angiogenetic activity comprising a pharmaceutically acceptable carrier and/or diluent and, as an active principle, a compound of formula (I), as defined above, or a pharmaceutically acceptable salt thereof.

20 The term tetralin is meant to refer to a 5,6,7,8-tetrahydronaphthalene ring.

The oxidolylidene substituent is preferably linked to position 1 or 2 of the naphthalene or tetralin ring, to position 4 or 5 of the quinoline ring, to position 5 or

25 8 of the isoquinoline ring and to position 2 or 3 of the indole ring, in particular to position 3.

The  $R_2$  substituent is preferably on the benzene moiety

-4-

when Y is indole.

The OR<sub>1</sub> groups and the oxindolylidene radical are preferably on the same benzene moiety when Y is naphthalene.

5 The OR<sub>1</sub> groups are preferably on the benzene moiety of the quinoline, isoquinoline or indole ring, whereas the oxindolylidene radical may be independently on either of the aryl or heteroaryl moiety of said bicyclic ring system.

10 When n is 2 or 3, the OR groups may be the same or different.

An OR<sub>1</sub> substituent is preferably linked to position 2, 3 or 4 when Y is 1-tetralyl or 1-naphthyl; it is preferably linked to position 1, 3 or 4 when Y is 2-tetralyl or 2-naphthyl. An OR<sub>1</sub> substituent is preferably linked to position 6, 7 or 8 when Y is 4- or 5-quinolyl.

15 An OR<sub>1</sub> substituent is preferably linked to position 4, 5, 6 or 7 when Y is 2- or 3-indolyl, in particular to position 5.

20 Of course only one of the substituents OR<sub>1</sub>, R<sub>2</sub> and oxindolylidene can be linked to the same position in the bicyclic ring system Y.

The R<sub>4</sub> substituent is preferably linked to position 4 or 5, in particular to position 5.

25 When Y is indole and R<sub>4</sub> is carboxy, nitro or NHR, in which R is as defined above, the R<sub>2</sub> substituent preferably has not the same meanings. Vice versa, when

-5-

R<sub>2</sub> is carboxy, nitro or NHR, in which R is as defined above, the R<sub>4</sub> substituent preferably is other than carboxy, nitro or NHR.

The alkyl groups, and the alkyl moiety in the alkanoyl groups, may be branched or straight alkyl chains. A C<sub>1</sub>-C<sub>6</sub> alkyl group is preferably a C<sub>1</sub>-C<sub>4</sub> alkyl group, e.g. methyl, ethyl, propyl, isopropyl, butyl, sec-butyl or tert-butyl, in particular methyl or ethyl.

A C<sub>2</sub>-C<sub>6</sub> alkanoyl group is preferably a C<sub>2</sub>-C<sub>4</sub> alkanoyl group, in particular acetyl, propionyl or butyryl.

A halogen is preferably chlorine, bromine or fluorine, in particular fluorine.

The invention also includes within its scope all the possible isomers, stereoisomers, in particular Z- and E-isomers and their mixtures, and the metabolites and the metabolic precursors or bio-precursors (otherwise known as pro-drugs) of the compounds of formula (I).

As already said, the invention includes within its scope also the pharmaceutically acceptable salts of the compounds of formula (I).

Pharmaceutically acceptable salts of the compounds of the invention include acid addition salts, with inorganic, e.g. nitric, hydrochloric, hydrobromic, sulphuric, perchloric and phosphoric acids, or organic, e.g. acetic, propionic, glycolic, lactic, oxalic, malonic, malic, maleic, tartaric, citric, benzoic, cinnamic, mandelic and salicylic acids, and salts with

-6-

inorganic, e.g. alkali metal, especially sodium or potassium, bases or alkaline-earth metal, especially calcium or magnesium bases, or with organic bases, e.g. alkylamines, preferably triethyl-amine.

5 As stated above, the present invention also includes within its scope pharmaceutically acceptable bio-precursors (otherwise known as pro-drugs) of the compounds of formula (I), i.e. compounds which have a different formula to formula (I) above, but which  
10 nevertheless upon administration to a human being are converted directly or indirectly in vivo into a compound of formula (I).

Preferred compounds of formula (I) are those wherein, subject to the above proviso, Y is naphthalene,  
15 tetralin, quinoline or indole and wherein when Y is naphthalene, tetralin or quinoline, then n is zero, 1 or 2; and

R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub> and R<sub>5</sub> are hydrogen; whereas when Y is indole, then  
20 n is zero or 1;  
R<sub>1</sub> is hydrogen or C<sub>1</sub>-C<sub>4</sub> alkyl;  
R<sub>2</sub> is hydrogen, amino, carboxy, cyano or C<sub>1</sub>-C<sub>4</sub> alkyl;  
R<sub>3</sub> and R<sub>5</sub> are hydrogen; and the pharmaceutically acceptable salts thereof.

-7-

Examples of specific preferred compounds of formula (I) are:

3-[(2'-naphthyl)methylen]-2-oxindole

m.p.: 207-209°

5 IR: 3300-3100 (NH), 1720 (CO), 1630, 1620  $\text{cm}^{-1}$ ;

3-[(1'-hydroxy-2'-naphthyl)methylen]-2-oxindole

IR: 3500-3100 (OH, NH), 1680 (CO)  $\text{cm}^{-1}$ ;

3-[(3'-hydroxy-2'-naphthyl)methylen]-2-oxindole;

3-[(4'-hydroxy-2'-naphthyl)methylen]-2-oxindole;

10 3-[(1'-naphthyl)methylen]-2-oxindole

m.p.: 179-81°

IR: 3500-3100 (OH, NH), 1680 (CO), 1610, 1560  $\text{cm}^{-1}$ ;

3-[(2'-hydroxy-1'-naphthyl)methylen]-2-oxindole;

3-[(3'-hydroxy-1'-naphthyl)methylen]-2-oxindole;

15 3-[(4'-hydroxy-1'-naphthyl)methylen]-2-oxindole

IR: 3500-3100 (NH, OH), 1680 (CO), 1610, 1570, 1510  $\text{cm}^{-1}$ ;

3-[(3'-hydroxy-1'-tetralyl)methylen]-2-oxindole;

3-[(4'-hydroxy-1'-tetralyl)methylen]-2-oxindole;

3-[(2'-hydroxy-1'-tetralyl)methylen]-2-oxindole;

20 3-[(1'-tetralyl)methylen]-2-oxindole;

3-[(2'-tetralyl)methylen]-2-oxindole;

3-[(1'-hydroxy-2'-tetralyl)methylen]-2-oxindole;

3-[(3'-hydroxy-2'-tetralyl)methylen]-2-oxindole

IR: 3500-3100 (NH, OH), 1685 (CO), 1610, 1570 (C=C)  $\text{cm}^{-1}$ ;

25 3-[(4'-hydroxy-2'-tetralyl)methylen]-2-oxindole;

3-[(1',4'-dihydroxy-2'-tetralyl)methylen]-2-oxindole

IR: 3500-3100 (OH, NH), 1680 (CO), 1620  $\text{cm}^{-1}$ ;

-8-

3-[(2-quinolyl)methylen]-2-oxindole

IR: 3180 (NH), 1710 (CO), 1620, 1595, 1505 (C=C) cm<sup>-1</sup>;

3-[(4-hydroxy-2-quinolyl)methylen]-2-oxindole;

3-[(3-quinolyl)methylen]-2-oxindole

5 IR: 3500-3100 (NH), 1695 (CO), 1620, 1580 (C=C, C=N);

3-[(4-quinolyl)methylen]-2-oxindole

m.p.: 277-9°

IR: 3300-2600 (NH), 1710 (CO), 1640, 1620, 1570 cm<sup>-1</sup>;

3-[(5-quinolyl)methylen]-2-oxindole;

10 3-[(6-hydroxy-5-quinolyl)methylen]-2-oxindole;

3-[(7-hydroxy-5-quinolyl)methylen]-2-oxindole;

3-[(8-hydroxy-5-quinolyl)methylen]-2-oxindole

m.p.: 282-4°

IR: 3400-2800 (NH, OH), 1690 (CO), 1670, 1610 (C=C) cm<sup>-1</sup>;

15 3-[(6-quinolyl)methylen]-2-oxindole;

3-[(5-hydroxy-6-quinolyl)methylen]-2-oxindole;

3-[(7-hydroxy-6-quinolyl)methylen]-2-oxindole;

3-[(8-hydroxy-6-quinolyl)methylen]-2-oxindole;

5-hydroxy-3-[(3'-indolyl)methylen]-2-oxindole

20 IR: 3600-2500 (NH, OH), 1650 (CO), 1600, 1580 cm<sup>-1</sup>;

3-[(5'-carboxy-3'-indolyl)methylen]-2-oxindole

IR: 3600-2100 (NH, OH), 1710 (CO), 1640, 1620, 1600 (atom);

3-[(5'-amino-3'-indolyl)methylen]-2-oxindole

IR: 3300, 2380 (NH), 1670 (CO), 1600, 1510 (C=C);

25 5-carboxy-3-[(3'-indolyl)methylen]-2-oxindole;

5-amino-3-[(3'-indolyl)methylen]-2-oxindole;

5-hydroxy-3-[(5'-hydroxy-3'-indolyl)methylen]-2-oxindole

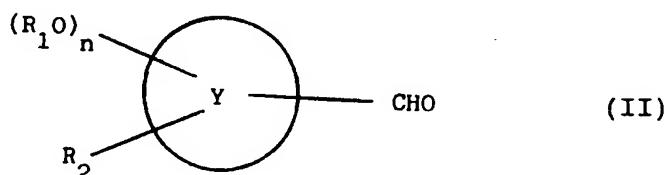
-9-

IR: 3600-2600 (NH,OH), 1655 (CO), 1605,1585 (C=C);  
5-hydroxy-3-[ (7'-hydroxy-3'-indolyl)methylen]-2-oxindole;  
3-[ (5',7'-dihydroxy-3'-indolyl)methylen]-2-oxindole;  
5 5-amino-3-[ (5'-hydroxy-3'-indolyl)methylen]-2-oxindole;  
5-hydroxy-3-[ (5'-amino-3'-indolyl)methylen]-2-oxindole;  
5-carboxy-3-[ (5'-hydroxy-3'-indolyl)methylen]-2-oxindole;  
5-hydroxy-3-[ (5'-carboxy-3'-indolyl)methylen]-2-  
10 oxindole;  
5-amino-3-[ (7'-hydroxy-3'-indolyl)methylen]-2-oxindole;  
5-carboxy-3-[ (7'-hydroxy-3'-indolyl)methylen]-2-oxindole;  
5-methoxy-3-[ (5'-methoxy-3'-indolyl)methylen]-2-  
15 oxindole;  
5-acetoxy-3-[ (5'-acetoxy-3'-indolyl)methylen]-2-oxindole;  
3-[ (5'-carboxy-3'-indolyl)methylen]-2-oxindole;  
3-[ (5'-amino-3'-indolyl)methylen]-2-oxindole;  
20 3-[ (5'-nitro-3'-indolyl)methylen]-2-oxindole;  
3-[ (1'-methyl-3'-indolyl)methylen]-2-oxindole;  
3-[ (3'-indolyl)methylen]-1-methyl-2-oxindole  
m.p.: 230°  
IR: 3300-2000 (NH), 1680 (CO), 1610,1600,1570 (C=C);  
25 if the case, either as single Z- or E- diastereoisomers  
or as a mixture thereof; and the pharmaceutically  
acceptable salts thereof.

-10-

The compounds of formula (I) according to the present invention, and the salts thereof, are known compounds and can be prepared by a process comprising reacting a compound of formula (II)

5



wherein Y, R<sub>1</sub>, R<sub>2</sub> and n are as defined above, with a compound of formula (III)

10       wherein R<sub>3</sub>, R<sub>4</sub> and R<sub>5</sub> are as defined above, using the methods and conditions as disclosed in the aforesaid international patent applications WO. 91/13055 and WO. 93/01182.

15       The compounds of formulae (II) and (III) are known or may be obtained as described in the aforesaid patent applications.

#### PHARMACOLOGY

The compounds of the invention have been found to be

-11-

active as angiogenesis inhibitors.

An angiogenesis inhibitor is an agent capable of suppressing the growth of new blood vessels. Therefore, the compounds of the present invention are useful in  
5 treating several pathological conditions in mammals, including humans, where the growth of new blood vessels is detrimental, for example in chronic inflammation, diabetic retinopathy, psoriasis, rheumatoid arthritis, tumor growth, in particular solid tumors, and  
10 development of metastases.

In particular, in cancer therapy the compounds of the invention can be administered alone or in association with an antitumor agent as herebelow defined.

The angiogenesis inhibitor activity of the compounds of  
15 the present invention is shown, e.g., by the fact that they have been found to be active in the chorioallantoic membrane (CAM) test according to the Folkman's method [Nature. 297, 307 (1982)].

For instance, the representative compound of the  
20 invention 3-[(1',4'-dihydroxy-2'-tetralyl)methylen]-2-oxindole, internal code FCE 26806, when tested in the CAM assay provided 87% positive CAMs, with inhibition area at 40  $\mu$ mol/pellet.

In addition, FCE 26806 was found to be active in the  
25 collagen gel assay as described by R. Montesano et al. in Cell 42, 469 (1985), inhibiting the invasion of the endothelial cells in a dose-dependent manner (43% and

-12-

22% inhibition at the concentration of 20 and 10  $\mu$ M, respectively).

The compounds of the invention can be administered in a variety of dosage forms, e.g. orally, in the form of 5 tablets, capsules, sugar or film-coated tablets, liquid solutions or suspensions; rectally, in the form of suppositories; parenterally, e.g. intramuscularly, or by intravenous injection or infusion; or topically.

10 The dosage depends on the age, weight, condition of the patient and administration route; for example, the dosage adopted for oral administration of the compound 3-[(1,4-dihydroxy-2'-tetralyl)methylen]-2-oxindole to adult humans may range from about 5 to about 150-200 mg per dose, from 1 to 5 times daily. Of course, these 15 dosage regimens may be adjusted to provide the optimal therapeutic response.

18 The pharmaceutical compositions according to the invention are usually prepared following conventional methods and are administered in a pharmaceutically suitable form.

For example, the solid oral forms may contain, together with the active compound, diluents, e.g., lactose, dextrose, saccharose, cellulose, corn starch or potato starch; lubricants, e.g., silica, talc, stearic acid, 25 magnesium or calcium stearate, and/or polyethylene glycols; binding agents, e.g., starches, arabic gums, gelatin, methylcellulose, carboxymethylcellulose or

-13-

polyvinyl pyrrolidone; disaggregating agents, e.g. a starch, alginic acid, alginates or sodium starch glycolate, effervescent mixtures; dyestuffs; sweeteners; wetting agents, such as lecithin, polysorbates, 5 laurylsulphates; and, in general, non-toxic and pharmacologically inactive substances used in pharmaceutical formulations. Said pharmaceutical preparations may be manufactured in known manner, for example, by means of mixing, granulating, tabletting, 10 sugar-coating or film-coating processes.

The liquid dispersion for oral administration may be, e.g., syrups, emulsions and suspensions.

The syrup may contain as carrier, for example, saccharose or saccharose with glycerine and/or mannitol 15 and/or sorbitol.

The suspensions and the emulsions may contain as carrier, for example, a natural gum, agar, sodium alginate, pectin, methylcellulose, carboxymethyl-cellulose or polyvinyl alcohol.

20 The suspensions or solutions for intramuscular injections may contain, together with the active compound, a pharmaceutically acceptable carrier, e.g. sterile water, olive oil, ethyl oleate, glycols, e.g. propylene glycol, and, if desired, a suitable amount of 25 lidocaine hydrochloride.

The solutions for intravenous injections or infusions may contain as carrier, for example, sterile water or,

-14-

preferably, they may be in the form of sterile, aqueous, isotonic saline solutions.

The suppositories may contain, together with the active compound, a pharmaceutically acceptable carrier, e.g.

5       cocoa-butter, polyethylene glycol, a polyoxyethylene sorbitan fatty acid ester surfactant or lecithin.

Compositions for topical application, e.g., creams, lotions, or pastes, can be prepared by mixing the active ingredient with a conventional oleaginous or emulsifying

10      excipient.

A further object of the present invention is a combined method of treatment of the above mentioned pathological conditions in mammals, including humans, in need of such treatment, said method comprising administering

15      1) an angiogenesis inhibitor according to the invention, or a pharmaceutically acceptable salt thereof, and

2) a different pharmaceutically active agent, typically an antitumor agent, in amounts and close enough together in time sufficient to produce a

20      therapeutically useful effect.

The present invention also provides products containing an angiogenesis inhibitor of the invention, or a pharmaceutically acceptable salt thereof, and an antitumor agent as a combined preparation for simultaneous, separate or sequential use in anti-cancer therapy.

25      The term "antitumor agent" is meant to comprise both a

-15-

single antitumor drug and "cocktails", i.e. a mixture of such drugs, according to clinical practice.

Examples of antitumor agents that can be formulated with an angiogenesis inhibitor according to the invention or 5 alternatively, can be administered in a combined method of treatment, include doxorubicin, daunomycin, epirubicin, idarubicin, etoposide, fluorouracil, mephalan, cyclophosphamide, bleomycin, vinblastine and mitomycin and mixtures of two or more thereof.

10 The angiogenesis inhibitors of the invention can therefore be used in a treatment to ameliorate a cancer. They may be administered to a patient suffering from a cancer treatable with an antitumor agent, for example an anthracycline glycoside such as doxorubicin, daunomycin, 15 epirubicin or idarubicin as mentioned above, together with the antitumor agent.

An angiogenesis inhibitor of the invention alone or in association with an antitumor agent such as an anthracycline glycoside can be therefore administered to 20 improve the condition of a patient having a leukaemia such as myeloblastic leukaemia, lymphoma, sarcoma, neuroblastoma, Wilm's tumor or malignant neoplasm of the bladder, breast, lung or thyroid.

The following examples of pharmaceutical formulations 25 illustrate but do not limit the present invention.

Example 1

-16-

Tablets each weighing 0.150 g and containing 25 mg of the active substance, can be manufactured as follows: composition (for 10,000 tablets):

3-[ (3'-hydroxy-2'-tetrallyl)methylen]-

5	2-oxindole	250 g
	Lactose	800 g
	Corn starch	415 g
	Talc powder	30 g
	Magnesium stearate	5 g

10 The 3-[ (3'-hydroxy-2'-tetrallyl)methylen]-2-oxindole, the lactose and half the corn starch are mixed; the mixture is then forced through a sieve of 0.5 mm mesh size. Corn starch (10 g) is suspended in warm water (90 ml) and the resulting paste is used to granulate the 15 powder. The granulate is dried, comminuted on a sieve of 1.4 mm mesh size, then the remaining quantity of starch, talc and magnesium stearate are added, carefully mixed and processed into tablets.

Example 2

20 Capsules, each dosed at 0.200 g and containing 20 mg of the active substance can be prepared.

Composition for 500 capsules:

3-[ (1',4'-dihydroxy-2'-tetrallyl)methylen]-

-17-

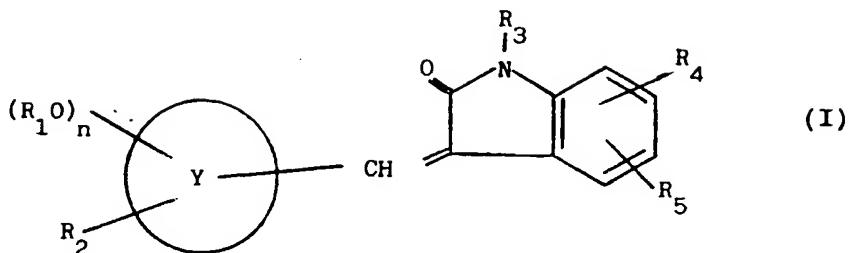
2-oxindole	10 g
Lactose	80 g
Corn starch	5 g
Magnesium stearate	5 g

5 This formulation is encapsulated in two-piece hard gelatin capsules and dosed at 0.200 g for each capsule.

-18-

CLAIMS

## 1. The use of a compound of formula (I)



wherein

5      Y    is a bicyclic ring selected from naphthalene, tetralin, quinoline, isoquinoline and indole;

    n    is zero or an integer of 1 to 3;

    R<sub>1</sub>  is hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl or C<sub>2</sub>-C<sub>6</sub> alkanoyl;

    R<sub>2</sub>  is hydrogen, halogen, C<sub>1</sub>-C<sub>6</sub> alkyl, cyano, carboxy, 10      nitro, or NHR, wherein R is hydrogen or C<sub>1</sub>-C<sub>6</sub> alkyl;

    R<sub>3</sub>  is hydrogen or C<sub>1</sub>-C<sub>6</sub> alkyl;

    R<sub>4</sub>  is hydrogen, hydroxy, C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>2</sub>-C<sub>6</sub> alkanoyloxy, carboxy, nitro or NHR, wherein R is 15      as defined above;

    R<sub>5</sub>  is hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl or halogen; or a pharmaceutically acceptable salt thereof;

    and wherein when Y is naphthalene then n is zero or an integer of 1 to 3, whereas when Y is tetralin, 20      quinoline, isoquinoline or indole then n is zero, 1 or 2; and wherein when the bicyclic ring Y is

-19-

naphthalene, quinoline, isoquinoline or indole, then each of the substituents OR<sub>1</sub>, R<sub>2</sub> and oxindolylidene may be independently on either of the aryl or heteroaryl moieties of said bicyclic ring, whereas 5 only the benzene moiety is substituted when Y is tetralin; and wherein when Y is naphthalene, tetralin, quinoline or isoquinoline, then R<sub>2</sub> is hydrogen, halogen, cyano or C<sub>1</sub>-C<sub>6</sub> alkyl and R<sub>3</sub>, R<sub>4</sub> and R<sub>5</sub> are 10 hydrogen; whereas when Y is indole, then R<sub>2</sub> is hydrogen, halogen, C<sub>1</sub>-C<sub>6</sub> alkyl, cyano, carboxy, nitro or -NHR, in which R is as defined above, R<sub>3</sub> is hydrogen or C<sub>1</sub>-C<sub>6</sub> alkyl, R<sub>4</sub> is hydrogen, hydroxy, C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>2</sub>-C<sub>6</sub> alkanoyloxy, carboxy, nitro or -NHR, 15 wherein R is as defined above, and R<sub>5</sub> is hydrogen, halogen or C<sub>1</sub>-C<sub>6</sub> alkyl; in the preparation of a medicament for use as anti-angiogenic agent.

2. The use of a compound of formula (I), or a salt thereof, according to claim 1, wherein in said 20 compound

Y is naphthalene, tetralin, quinoline or indole, and wherein when

Y is naphthalene, tetralin or quinoline, then n is zero 1 or 2; and

25 R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub> and R<sub>5</sub> are hydrogen; whereas when Y is indole, then

-20-

n is zero or 1;

R<sub>1</sub> is hydrogen or C<sub>1</sub>-C<sub>4</sub> alkyl;

R<sub>2</sub> is hydrogen, amino, carboxy, cyano or C<sub>1</sub>-C<sub>4</sub> alkyl;

and

5 R<sub>3</sub> and R<sub>5</sub> are hydrogen.

3. The use of a compound or formula (I) according to claim 1 wherein said compound is chosen from

3-[(2'-naphthyl)methylen]-2-oxindole;

3-[(1'-hydroxy-2'-naphthyl)methylen]-2-oxindole;

10 3-[(3'-hydroxy-2'-naphthyl)methylen]-2-oxindole;

3-[(4'-hydroxy-2'-naphthyl)methylen]-2-oxindole;

3-[(1'-naphthyl)methylen]-2-oxindole;

3-[(2'-hydroxy-1'-naphthyl)methylen]-2-oxindole;

3-[(3'-hydroxy-1'-naphthyl)methylen]-2-oxindole;

15 3-[(4'-hydroxy-1'-naphthyl)methylen]-2-oxindole;

3-[(3'-hydroxy-1'-tetracyl)methylen]-2-oxindole;

3-[(4'-hydroxy-1'-tetracyl)methylen]-2-oxindole;

3-[(2'-hydroxy-1'-tetracyl)methylen]-2-oxindole;

3-[(1'-tetracyl)methylen]-2-oxindole;

20 3-[(2'-tetracyl)methylen]-2-oxindole;

3-[(1'-hydroxy-2'-tetracyl)methylen]-2-oxindole;

3-[(3'-hydroxy-2'-tetracyl)methylen]-2-oxindole;

3-[(4'-hydroxy-2'-tetracyl)methylen]-2-oxindole;

3-[(1',4'-dihydroxy-2'-tetracyl)methylen]-2-oxindole;

25 3-[(2-quinolyl)methylen]-2-oxindole;

3-[(4-hydroxy-2-quinolyl)methylen]-2-oxindole;

-21-

3-[(3-quinolyl)methylen]-2-oxindole;  
3-[(4-quinolyl)methylen]-2-oxindole;  
3-[(5-quinolyl)methylen]-2-oxindole;  
3-[(6-hydroxy-5-quinolyl)methylen]-2-oxindole;  
5 3-[(7-hydroxy-5-quinolyl)methylen]-2-oxindole;  
3-[(8-hydroxy-5-quinolyl)methylen]-2-oxindole;  
3-[(6-quinolyl)methylen]-2-oxindole;  
3-[(5-hydroxy-6-quinolyl)methylen]-2-oxindole;  
3-[(7-hydroxy-6-quinolyl)methylen]-2-oxindole;  
10 3-[(8-hydroxy-6-quinolyl)methylen]-2-oxindole;  
5-hydroxy-3-[(3'-indolyl)methylen]-2-oxindole;  
3-[(5'-carboxy-3'-indolyl)methylen]-2-oxindole;  
3-[(5'-amino-3'-indolyl)methylen]-2-oxindole;  
5-carboxy-3-[(3'-indolyl)methylen]-2-oxindole;  
15 5-amino-3-[(3'-indolyl)methylen]-2-oxindole;  
5-hydroxy-3-[(5'-hydroxy-3'-indolyl)methylen]-2-  
oxindole;  
5-hydroxy-3-[(7'-hydroxy-3'-indolyl)methylen]-2-  
oxindole;  
20 3-[(5',7'-dihydroxy-3'-indolyl)methylen]-2-oxindole;  
5-amino-3-[(5'-hydroxy-3'-indolyl)methylen]-2-  
oxindole;  
5-hydroxy-3-[(5'-amino-3'-indolyl)methylen]-2-  
oxindole;  
25 5-carboxy-3-[(5'-hydroxy-3'-indolyl)methylen]-2-  
oxindole;  
5-hydroxy-3-[(5'-carboxy-3'-indolyl)methylen]-2-

-22-

oxindole;

5-amino-3-[ (7'-hydroxy-3'-indolyl)methylen]-2-oxindole;

5-carboxy-3-[ (7'-hydroxy-3'-indolyl)methylen]-2-oxindole;

5-methoxy-3-[ (5'-methoxy-3'-indolyl)methylen]-2-oxindole;

5-acetoxy-3-[ (5'-acetoxy-3'-indolyl)methylen]-2-oxindole;

10 3-[ (5'-carboxy-3'-indolyl)methylen]-2-oxindole;

3-[ (5'-amino-3'-indolyl)methylen]-2-oxindole;

3-[ (5'-nitro-3'-indolyl)methylen]-2-oxindole;

3-[ (1'-methyl-3'-indolyl)methylen]-2-oxindole;

3-[ (3'-indolyl)methylen]-1-methyl-2-oxindole;

15 if the case, either as single Z- or E-diastereoisomers or as a mixture thereof; or a pharmaceutically acceptable salt thereof.

4. A compound of formula (I) or a pharmaceutically acceptable salt thereof, as defined in claim 1, for 20 use in the inhibition of angiogenesis in mammals.

5. A pharmaceutical composition having anti-angiogenic activity comprising a pharmaceutically acceptable carrier and/or diluent and as an active principle a compound of formula (I) as defined in claim 1, or a 25 pharmaceutically acceptable salt thereof.

-23-

6. A combined method of treatment in mammals of a pathological condition where the growth of new vessels is detrimental, said method comprising administering

5        1) an angiogenesis inhibitor, as defined in claim 1, or a pharmaceutically acceptable salt thereof, and  
2) a different pharmaceutically active agent, in amounts and close enough together in time sufficient to produce a therapeutically useful  
10        effect.

15        7. Products containing an angiogenesis inhibitor as defined in claim 1, or a pharmaceutically acceptable salt thereof, and an antitumor agent as a combined preparation for simultaneous, separate or sequential use in anti-cancer therapy.

20        8. A method of treating a pathological condition where the growth of new blood vessels is detrimental, comprising administering to a host suffering from said pathological condition a therapeutically effective amount of a compound of formula (I), as defined in claim 1, or a pharmaceutically acceptable salt thereof.

## INTERNATIONAL SEARCH REPORT

International Application No  
PCT/EP 94/03664A. CLASSIFICATION OF SUBJECT MATTER  
IPC 6 A61K31/40 A61K31/405 A61K31/70 A61K31/71

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)  
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO,A,93 01182 (FARMITALIA CARLO ERBA) 21 January 1993 cited in the application see page 16 - page 17; claims 1-10	4,5,7
Y	see the whole document cited in the application ---	1-3,6,8
X	WO,A,91 13055 (FARMITALIA CARLO ERBA S.R.L.) 5 September 1991 cited in the application see claims 1-8	4,5,7
Y	see the whole document cited in the application ---	1-3,6,8
Y	WO,A,92 21660 (PFIZER INC.) 10 December 1992 see page 1, line 1 - line 6 ---	1-8 -/-

 Further documents are listed in the continuation of box C. Patent family members are listed in annex.

## \* Special categories of cited documents :

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

- \*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- \*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- \*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- \*&\* document member of the same patent family

Date of the actual completion of the international search  15 February 1995	Date of mailing of the international search report  - 1. 03. 95
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+ 31-70) 340-3016	Authorized officer  Uiber, P

## INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 94/03664

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,Y	WO,A,94 14808 (FARMITALIA CARLO ERBA S.R.L) 7 July 1994 see page 12, line 14 - page 13, line 20; claims 10,11 ----	1-8
P,Y	WO,A,94 03427 (WARNER-LAMBERT COMP.) 17 February 1994 see page 21, line 14 - line 22; claim 1 -----	1-8

## INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 94/03664

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO-A-9301182	21-01-93	AU-B-	656015	19-01-95
		AU-A-	2277792	11-02-93
		CA-A-	2091058	13-01-93
		EP-A-	0525472	03-02-93
		EP-A-	0552329	28-07-93
		JP-T-	6501494	17-02-94
WO-A-9113055	05-09-91	AU-B-	652740	08-09-94
		AU-A-	7241291	18-09-91
		EP-A-	0470221	12-02-92
		JP-T-	4506081	22-10-92
		NZ-A-	237182	23-12-93
		US-A-	5374652	20-12-94
WO-A-9221660	10-12-92	CA-A-	2108889	30-11-92
		EP-A-	0586608	16-03-94
		JP-T-	6503095	07-04-94
WO-A-9414808	07-07-94	AU-B-	5810594	19-07-94
		CA-A-	2126228	07-07-94
		CN-A-	1093707	19-10-94
		EP-A-	0626963	07-12-94
		FI-A-	943838	19-08-94
WO-A-9403427	17-02-94	AU-B-	4799493	03-03-94